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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/903,410	07/10/2001	Dan E. Robertson	DIVER1180-2	8980

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EXAMINER	
PROUTY, REBECCA E	
ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 10/25/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

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Office Action Summary	Application No.	Applicant(s)	
	09/903,410	ROBERTSON ET AL.	
	Examiner	Art Unit	
	Rebecca E. Prouty	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *42-55,61-63,65 and 88-92* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5, 16, 20-23, 40-41, 67, 68, 77, 78, 80-82, 85, 97-102, 107-111, 113-117, 126-129* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 1-5,16,20-23,40-55,61-63,65,67,68,80-82,88-92,98-102,107-111,113-117 and 126-129.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/19/06 has been entered.

Claims 6-15, 17-19, 24-39, 56-60, 64, 66, 69-79, 83-87, 93-97, 103-106, 112 and 118-125 have been canceled. Claims 1-5, 16, 20-23, 40-55, 61-63, 65, 67, 68, 80-82, 88-92, 98-102, 107-111, 113-117, 126 and newly presented claims 127-129 are still at issue and are present for examination.

Applicants' arguments filed on 7/19/06, have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claims 42-55, 61-63, 65 and 88-92 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the response filed 6/2/03.

Claims 1-5, 16, 20-23, 40-41, 67, 68, 77, 78, 80-82, 85, 97-102, 107-111, 113-117, 126 and newly presented claims 127-129 are examined herein.

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

This application is claiming the benefit of prior-filed nonprovisional application No. PCT/US97/02039 under 35 U.S.C. 120, 121, or 365(c). Copendency between the current application and the prior application is required. Since the applications are not copending, the benefit claim to the prior-filed nonprovisional application is improper. Applicant is required to delete the reference to the prior-filed application from the first sentence(s) of the specification, or the application data sheet, depending on where the reference was originally submitted, unless applicant can establish copendency between the applications.

Claim 4 is objected to because of the following informalities: the word "the should be inserted following "wherein" in line 4. Appropriate correction is required.

Claims 1-5, 16, 20, 21, 40, 41, 67, 68, 80-82, 98-102, 107-111, 113-117, and 126-129 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-5, 16, and 67 (upon which claims 20, 40, 41, 68, 80, 81, 98-102, 107-111, 113-117, and 126 depend) are indefinite in the recitation of "complementary to" a reference sequence as it is unclear if this term includes only the full length complement of the reference sequence or encompasses sequences complementary to only a portion of the reference sequence. For purposes of further examination it is presumed that this was intended to only include the full length complement.

Claims 21, 82, and 127-129 are indefinite in the recitation of "at least about" as the terms "at least" and "about" are inconsistent with each other.

Claims 1, 3-5, 16, 20-23, 40, 41, 67, 68, 80-82, 98-102, 107-111, 113-117 and 126-129 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the

claimed invention. The rejection is explained in the previous Office Action.

Claims 1, 22 are directed to polynucleotides having 90% sequence identity to SEQ ID NO:26 and encoding a polypeptide with an esterase activity or polynucleotides encoding a protein having 90% sequence identity to SEQ ID NO:36 while claims 20, 21 and 127 are directed to polynucleotides having 95% (and 97 or 98%) sequence identity to SEQ ID NO:26 and encoding a polypeptide with an esterase activity and claims 128-129 are directed to polynucleotides encoding proteins having 95% (or 98%) sequence identity to SEQ ID NO:36 and esterase activity. Claims 3-5, 107-109 and 126 are directed to polynucleotides which will hybridize to SEQ ID NO:26 under specified conditions and encode a polypeptide with an esterase activity. Claims 40, and 98-102 recite vectors and host cells comprising said nucleic acids or methods of expressing said nucleic acids. As discussed in the written description guidelines the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed

correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. A representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. The claimed genera recited in claims 1, 3-5, 20-22, 40, 98-102, 107-109, and 126-129 is enormously variable in functional characteristics in view of the broad scope of the term esterase. All members of the genus will not catalyze the same reaction. Yet the specification describes completely only the nucleic acid of SEQ ID NO:26 which encodes the esterase of SEQ ID NO:36. This single species is not representative of all members of the genus as others members of the genus will catalyze different enzymatic reactions than the esterase of SEQ ID NO:36. In order to fully describe the claimed genera the specification should describe species representative of other esterase reactions catalyzed by other species of the genus. The remainder of the claims recite even broader genera of nucleic acids than recited in Claims 1, 3-5, 20-22, 40, 98-102, 107-109, and 126-129. As such all discussion of Claims 1, 3-5, 20-22, 40, 98-102, 107-109, and 126-129

applies to these claims as well. However, these claims further include fragments and variants of the nucleic acids of Claims 1, 3-5, 20-22, 40, 98-102, 107-109, and 126-129 which completely lack any disclosed functional limitation at all. Applicants statements that that these nucleic acids can all be used as probes for the isolation and identification of esterase nucleic acids is not persuasive. The recited structural features of the claimed genera to not in fact provide a genus which all can be used as stated by applicants. The claimed polynucleotides will bind to both esterase encoding sequences (such as SEQ ID NO:26) and non-esterase encoding sequences (such as variants of SEQ ID NO:26 with single substitutions which encode catalytically inactive proteins).

Claims 1, 3-5, 16, 20-23, 40, 41, 67, 68, 80-82, 98-102, 107-111, 113-117 and 126 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for polynucleotides encoding SEQ ID NO:36, does not reasonably provide enablement for any polynucleotide having at least 90-98% sequence identity to SEQ ID NO:26 and encoding a polypeptide with <u>any</u> esterase activity, or any polynucleotide which will hybridize of SEQ ID NO:26 under defined conditions or any polynucleotide comprising at least 30 bases of a sequence having 90% identity to SEQ ID NO:26 and encoding a polypeptide having

esterase activity, or any polynucleotide comprising a fragment of SEQ ID NO:26 or encoding fragments of SEQ ID NO:36, or all fragments and variants thereof or vectors and host cells comprising said nucleic acids. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The rejection is explained in the previous Office Action.

Applicants argue that the teachings of Guo et al., previously cited by the Office are insufficient to rebut the presumptively enabled specification and therefore cannot support a *prima facie* case of lack of enablement. The narrowest of applicants claims that are rejected are those of Claims 1, 20-22 and 127-129. Claim 1 was specifically addressed in the Office Action of 5/5/05 which clearly explained why randomly making variants having only 90% identity to SEQ ID NO:26 and testing them for those retaining activity would be undue experimentation based on a numerical estimate of what percentage of such randomly constructed mutants would be active. It is well accepted in the art (and the data of Guo et al. shows experimentally) that tolerance to modification for a given protein diminishes in an exponential fashion with each further and additional modification while the numbers of possible

variants increases exponentially. As such what appear to be fairly small changes in the %identity to a specific sequence recited in a claim may well make large changes in the amount of experimentation necessary as well as the expectation of success such that the determination of whether it would require undue experimentation to make and use the full scope of what is claimed can be very different. Absent limitations to the scope of the claims such that randomly making variants and testing them for those retaining activity would not be undue experimentation, guidance regarding (A) regions of the protein structure which may be modified without effecting esterase activity; (B) the general tolerance of esterases to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residues with an expectation of obtaining the desired biological function; and (D) guidance as to which of the essentially enormous number of possible choices is likely to be successful is clearly necessary and is not provided by the instant specification. It is noted that current claims 20-22 and 127-129 are included in the instant rejection despite the structural limitation to a genus for which randomly making variants and testing them for those retaining activity would arguably (for Claim 20) and clearly (for Claims 21, 22 and 127-129) not be undue experimentation based on an

similar analysis using the numerical estimates of Guo et al. because the functional limitation (i.e., esterase activity) of these claims is so broad as to require screening all variants for not just one particular activity (as did Guo et al.) but to require they be screened for hundreds of distinct activities each. This would clearly still be undue experimentation. Limitation of these claims to a specific esterase activity to be screened for would overcome this rejection for claims 20-22. Applicants argue that nevertheless, while not necessary, if one skilled in the art desired some structural guidance as to what amino acid substitutions could be made to make the genus of esterase-encoding nucleic acids of the invention, such guidance could be found both in the specification and the state of the art at the time of the invention. For example, the specification provides express guidance regarding what amino acid substitutions could be made to make the genus of esterase encoding nucleic acids of the invention be in paragraphs [54] or [205] of the specification; and the prior art provides teachings regarding for example, active sites and structures of various polypeptides having esterase activity. However, this is not persuasive because the guidance provided in the specification is so general in nature as to add little or nothing to the predictability of which variants should be made and while the

art provides teachings with regard to active sites and structures of various polypeptides having esterase activity, the relevance of these to variants of SEQ ID NO:26 is highly questionable indeed as the protein encoded by the single disclosed species (i.e., SEQ ID NO:36) has little or no structural identity to the esterases discussed in the prior art. If such structural identity were present many of the claims would have been rejected under 35 U.S.C. 102 as the structural limitations of most of the claims are so limited that virtually any prior art teaching of a structurally related nucleic acid would be encompassed. The absence of any such rejections is due to the fact that the esterase encoded by SEQ ID NO:26 is substantially different than all prior art esterases. Applicants should note that **even** assuming that the guidance provided in the specification and art would be sufficient to alter the percentage of random single substitution mutations which inactivate the protein of SEQ ID NO:36 to be only 1 in 5, which seems highly unlikely given the lack of many similar esterases in the prior art (assuming the skilled artisan could avoid altering at least some highly conserved amino acids), this would still result in an alteration of the previous estimate given to the following: $(.8)^{75}$ X 100% or 5.4×10^{-6}% (i.e., approximately 1 in 18.5 million) mutants having 75 substitutions

in positions other than those highly conserved would be active. Current techniques in the art (i.e., high throughput mutagenesis and screening techniques) as are discussed in the declaration of Dr. Short would allow for finding a few active mutants within several hundred thousand or up to about a million inactive mutants (despite even this being an enormous quantity of experimentation that would take a very long time to accomplish) but finding a few mutants within multiple millions or more as in the current claims would not be possible and clearly would constitute undue experimentation. For all the reasons discussed above, the rejection for lack of enablement of the full scope of the invention is maintained.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 3, 5, 40, 82, 98-102, 107-109, 110-111, 114-117, 126, 127 and 129 rejected under 35 U.S.C. 102(b) as being anticipated by Robertson et al. (WO 97/30160). The rejection was explained in the previous Office Action.

Applicants traverse the rejection by arguing that the priority claim to PCT/WO97/02039 has been perfected and thus

Robertson et al. is not prior art. However, applicants renewed petition under 37 CFR 1.78(a)(3) or (a)(6) to obtain the benefit of PCT/US07/02039 was denied as the instant application was not copending with the PCT application at the time of filing. See the petition decision of 7/18/06. As such the rejection is maintained for the reasons of record.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rebecca E. Prouty whose telephone number is 571-272-0937. The examiner can normally be reached on Tuesday-Friday from 8 AM to 5 PM. The examiner can also be reached on alternate Mondays

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (571) 272-0928. The fax phone number for this Group is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Rebecca Prouty
Primary Examiner
Art Unit 1652